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On the observation of Hypokalemia in Covid-19

Amelia Carolina Sparavigna
Politecnico di Torino

Hypokalemia is a low level of potassium in the blood serum. Here a survey of literature about the observation of Hypokalemia in Covid-19. In particular we consider the study published in a MedRvix preprint "Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19)".

Keywords: Hypokalemia, Covid-19.

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In [1,2], we have considered some literature about Covid-19 Cytokine Release Syndrome, known as "cytokine storm", of drugs used for it and of a the possible use of Vitamin D for Covid-19.

Here we consider literature about the observation of Hypokalemia in Covid-19.

"Hypokalemia is a low level of potassium (K+) in the blood serum. Mild low potassium does not typically cause symptoms. Symptoms may include feeling tired, leg cramps, weakness, and constipation. Low potassium also increases the risk of an abnormal heart rhythm, which is often too slow and can cause cardiac arrest. ... Mild hypokalemia (>3.0 mEq/l) may be treated by eating potassium-containing foods or by taking potassium chloride supplements ... Eating potassium-rich foods may not be the optimal method for correcting low potassium ... Potassium chloride supplements by mouth have the advantage of containing precise quantities of potassium, ... the potential for side-effects including nausea and abdominal discomfort. Potassium bicarbonate is preferred when correcting hypokalemia associated with metabolic acidosis." https://en.wikipedia.org/wiki/Hypokalemia (in Italiano, Ipokaliemia oppure Ipopotassiemia. Attenzione: "Un eccesso di cloruro di potassio è tossico, può provocare iperkaliemia, aritmie e morte cardiaca improvvisa". https://it.wikipedia.org/wiki/Cloruro_di_potassio#Precauzioni)

Here some news and literature about Hypokalemia in Covid-19.

News - "Covid-19 Research Updates: Chinese Study Reveals That Hypokalemia Present In Almost All Covid-19 Patients". Source: Covid-19 Research Mar 09, 2020 - "Covid-19 Research: A new research study by researchers from Wenzhou Medical University in Zhejiang province lead by Dr Dong Chen revealed that almost all Covid-19 patients exhibited hypokalemia and that supplementation with potassium ions was one of the many factors that assisted in their recovery ... It was found that as the SARS-CoV-2 coronavirus attacks human cells via the ACE2 (Angiotensin-converting enzyme-2) receptors, it also attacks the renin–angiotensin system (RAS), causing low electrolyte levels in particularly potassium ions. The study involving 175 patients in collaboration with Wenzhou Hospital found that almost all patients exhibited hypokalemia and for those who already had hypokalemia, the situation even drastically worsened as the disease progressed. However, it was found from the study that patients responded well to potassium ion supplements and had a better chance of recovery". https://www.thailandmedical.news/news/covid-19-research-updates-chinese-study-reveals-that-hypokalemia-present-in-almost-all-covid-19-patients

This news is mentioning the following research article entitled "Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19)" [3]. Abstract tells that "SARS-CoV-2 binds angiotensin I converting enzyme 2 (ACE2) of renin-angiotensin system (RAS) and causes prevalent hypokalemia". "The patients with COVID-19 were classified into severe hypokalemia, hypokalemia, and normokalemia group. The study aimed to determine the

relationship between hypokalemia and clinical features, the underlying causes and clinical implications of hypokalemia". The results given in [3] are the following. "By Feb 15, 2020, 175 patients with COVID-19 (92 women and 83 men; median age, 46 [IQR, 34-54] years) were admitted to hospital in Wenzhou, China, consisting 39 severe hypokalemia-, 69 hypokalemia-, and 67 normokalemia patients. Gastrointestinal symptoms were not associated with hypokalemia among 108 hypokalemia patients ($P>0.05$). Body temperature, CK, CK-MB, LDH, and CRP were significantly associated with the severity of hypokalemia ($P<0.01$). 93% of severe and critically ill patients had hypokalemia which was most common among elevated CK, CK-MB, LDH, and CRP. Urine K+ loss was the primary cause of hypokalemia. severe hypokalemia patients was given 3 g/day, adding up to an average of 34 (SD=4) g potassium during hospital stay. The exciting finding was that patients responded well to K+ supplements when they were inclined to recovery". The conclusions of the researchers is that "Hypokalemia is prevailing in patients with COVID-19. The correction of hypokalemia is challenging because of continuous renal K+ loss resulting from the degradation of ACE2. The end of urine K+ loss indicates a good prognosis and may be a reliable, in-time, and sensitive biomarker directly reflecting the end of adverse effect on RAS system".

Data from [3] had been used in [4], where the authors "compared the prevalence of abnormal clinical indices of the paediatric patients with previously reported data for 175 adults with COVID-19 in Wenzhou," [3] "44 paediatric patients with SARS in Hong Kong, and 167 Chinese paediatric patients with H1N1 influenza".

Work [3] is mentioned in [5], where the authors tell "Urine potassium loss was the primary cause of hypokalemia, and it has been reported that SARS-CoV-2 binds angiotensin I converting enzyme 2 (ACE2) on the cell membrane A and promote the degradation of ACE2, and thus decreases the counter-act of ACE2 on renin–angiotensin system (RAS). This mechanism increase reabsorption of sodium and water, and increase the excretion of potassium (12) [3]. The authors [in MedRxiv] reported that the correction of hypokalemia was challenging because of the continuous loss of potassium, and for the cardiovascular effects and neurohormonal activation, and other vital organs by hypokalemia".

Work [3] is mentioned in [6]. "Electrolyte imbalances can occur in any critical systemic illness and precipitate arrhythmias, esp. in patients with underlying cardiac disorder. There is particular concern about hypokalemia in COVID-19, due to interaction of SARS-CoV-2 with renin-angiotensin-aldosterone system. Hypokalemia increases vulnerability to various tachyarrhythmias".

Work [3] is mentioned in [7]. In a quite long section of [7] it is told that "Patients with more severe COVID-19 are reported to have hypokalemia and higher blood pressure as compared with those with milder COVID-19 that would support a role for a stimulated ANG II-AT_1 receptor axis (6). Current clinical data on the ACE2-Ang-(1–7) pathway, however, are quite limited relative to the experimental data, especially in regard to the effects of ACEI and ARB. Furthermore, the existing evidence, though novel and insightful, often comes from smaller cross-sectional observational studies with incomplete RAAS measurements that cannot fully account for potential sources of bias and confounding".

News - "Do ACE inhibitors increase SARS-CoV-2 binding to ACE2?" - by Liji Thomas, https://www.news-medical.net/news/20200420/Do-ACE-inhibitors-increase-SARS-CoV-2-binding-to-ACE2.aspx 20 April 2020. "Dysregulation of Ang II - Many patients with COVID-19 have been reported to develop hypokalemia (low potassium). This is not due to any apparent loss through the gut and is proportional to the severity of the disease. However, the report on this condition did not mention the prevalence of the use of RAAS inhibitors as a confounding factor. Some see this as a complication of RAAS dysfunction in COVID-19. They suggest that the loss of potassium through the kidneys may be due to higher Ang II levels due to the binding of the SARS-CoV-2 virus to ACE2 receptors. This could, they think, prevent the action of ACE2 in maintaining the balance between ACE2 and Ang II levels. The ARB losartan was found to improve lung injury in mice by reducing levels of Ang II. When the genes for ACE2 are not expressed in a mouse model, and the

knockout mouse, as it is called, is exposed to viral influenza, the affected mice were sicker and less likely to survive. This could indicate the protective role of ACE2 in stabilizing Ang II levels, converting the latter to Ang 1-7".

Work [3] in mentioned in [8]. "Furthermore, a recently concluded study showed that severe and critically ill patients with COVID-19 had a higher prevalence of hypokalemia that resulted from renal potassium wasting. This can be explained by downregulation of ACE2 following viral intrusion resulting in decreased degradation of angiotensin-II, increased aldosterone secretion and subsequent increased urinary potassium loss. In fact early normalization of serum potassium has been proposed to be a predictor of good prognosis in COVID-19 [16]. Thus, ACE2 overexpression, while facilitating entry of SARS-CoV-2, is unable to protect against lung injury as the enzyme gets degraded by the virus (see Fig. 1) ".

Work [3] is mentioned in [9]. " In early COVID-19 studies, some evidence has been provided that electrolyte disorders may also be present upon patients' presentation, including sodium, potassium, chloride and calcium abnormalities. Others have postulated that patients with more severe COVID-19 tend to display a higher proportion of hypokalaemia at baseline compared with those with less severe forms of disease. [3] Such electrolyte disturbances have important implications not only for patient management but also for identifying potential pathophysiologic mechanisms underlying COVID-19, that could drive novel therapeutic opportunities. Nevertheless, limited sample sizes and heterogeneity in electrolyte reporting have limited interpretations to-date. Therefore, ...".

In [10], it is told that "There is particular concern about hypokalemia in COVID-19 disease; as a result interaction of SARS-CoV2 with the RAS system. Hypokalemia is well known to increases vulnerability to various kinds of arrhythmia". And also "There is particular concern about hypokalemia in COVID-19 disease; as a result interaction of SARS-CoV2 with the RAS system". In [10], the reference given points to [11], but it seems it is not the proper one. In any case, in [10] it is told that "Hypokalemia is well known to increases vulnerability to various kinds of arrhythmia. Recommendations for the management of arrhythmias follows a similar pattern for non-COVID patients with optimization of electrolytes, avoiding triggers including medication modification and EKG monitoring for patients with long QTc or on medications known to prolong QTc interval". Ref.10 mentions [12].

In [11], it is told, about Covid-19, that "Much has been learnt in the course of preceding epidemics, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza, and it is now recognized that their overall health burden may be under-estimated since extra-pulmonary manifestations are frequent. Acute and chronic cardiovascular complications of pneumonia are common and result from various mechanisms, including relative ischaemia, systemic inflammation, and pathogen-mediated damage. There is, however, only limited published data concerning cardiovascular presentations in the wake of viral epidemics. The present COVID-19 outbreak emphasizes the need for greater awareness of the immediate and long-term cardiovascular implications of viral infection and the significant gaps in knowledge that future research will need to address".

Let us conclude with news.

News - «Terapie a casa, un mix di farmaci Potassio e magnesio per il cuore» Per fare chiarezza su come affrontare l'infezione, Regione Lombardia ha istituito una Rete per la valutazione farmacologica e terapeutica dei pazienti con Covid-19 - Articolo di Laura Cuppini - 2 Aprile 2020 - https://www.corriere.it/salute/malattie_infettive/20_aprile_02/terapie-casa-mix-farmaci-potassio-magnesio-il-cuore-82314fac-744a-11ea-b181-d5820c4838fa.shtml

It is an interview with Francesco Scaglione, Università degli Studi di Milano and Ospedale Niguarda. The question is "Quali sono quindi i farmaci che funzionano davvero? «Siamo partiti da una riflessione: un ruolo-chiave è quello del meccanismo di eccessiva infiammazione associato a una sindrome da rilascio citochinico - for what concern the therapy - La combinazione è la

seguente: idrossiclorochina (un vecchio farmaco antimalarico), azitromicina (antibiotico con effetto immunomodulante) e celecoxib, antinfiammatorio con attività nei confronti della ciclo-ossigenasi di tipo 2 (COX-2, enzima che determina il rilascio di citochine). ... Tutti i pazienti dovrebbero assumere supplementi di potassio e magnesio per scongiurare il rischio di aritmie cardiache, possibile effetto collaterale della combinata idrossiclorochina-azitromicina».

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